REDACTED VERSION OF DOCUMENT(S) SOUGHT TO BE SEALED

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

FLUIDIGM CORPORATION, a Delaware corporation; and FLUIDIGM CANADA INC., a foreign corporation,

Plaintiffs,

v.

IONPATH, INC., a Delaware corporation,

Defendant.

Case No. 3:19-cv-05639

**PLAINTIFFS FLUIDIGM CORPORATION'S & FLUIDIGM CANADA INC.'S MOTION FOR SUMMARY JUDGMENT ON DIRECT INFRINGEMENT AND VALIDITY OF SHOWDOWN CLAIMS**

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Fluidigm Corporation and Fluidigm Canada Inc. (collectively "Fluidigm") hereby respectfully move the Court, pursuant to the Court's "showdown" schedule, to grant summary judgment that IONpath, Inc.'s ("IONpath") MIBIscope System ("MIBI")[1] infringes Claim 6 of U.S. Patent No. 10,180,386 (the "'386 Patent") (Ex. A) and Claim 9 of U.S. Patent No. 10,436,698 (the "'698 Patent") (Ex. B) and that these claims are valid.[2]

From the outset of this case, IONpath has repeatedly asserted that MIBI is fundamentally different from the inventions disclosed and claimed in the '386 and '698 Patents because MIBI is a "SIMS-based system [that] uses a mechanical process of 'sputtering' to knock loose the ions that will ultimately be detected." ECF No. 42 (Joint CMC Statement) at 5. IONpath's argument is founded on its proposed construction of "vaporize, atomize, and ionize" and that the asserted claims "expressly require the use of [] a heat source (such as an argon plasma) to vaporize, atomize and ionize a sample … ." *Id.* at 4. The problem with IONpath's advocacy is that it is false and directly contradicted by the claims themselves, IONpath's own documents and patents, and the numerous admissions of its expert witness.

In reality, persons of ordinary skill in the art ("POSITA") have used the term "vaporize, atomize, and ionize" to describe the "sputtering" of SIMS for decades (the same technique used by IONpath's MIBI). [redacted]. Equally compelling, IONpath marks its MIBI products with a patent filed by its founders that uses that ***precise*** language. Ex. D (U.S. Patent No. 9,312,111) at 10:40-43 ("The material associated with the sample segment is

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1/ [redacted]

2/ As the '386 and '698 Patents share a common specification, any citation to the '386 Patent specification should be treated, where appropriate, as including a citation to the corresponding specification of the '698 Patent (and vice-versa).

*vaporized, atomized and ionized* by the primary ion irradiation unit 1010, and secondary ions associated with the sample segment are produced." (emphasis added)). IONpath's other principal non-infringement argument, that MIBI does not perform single-cell analysis, is contradicted by its own marketing, which consistently states that MIBI does in fact perform "single-cell analysis." IONpath's core non-infringement positions are utterly frivolous. And IONpath's documents and the admissions of its expert witness establish infringement of all of the other claim elements.

Regarding validity, IONpath concedes that not a single piece of prior art anticipates the showdown claims. Instead, it resorts to mixing and matching a variety of unrelated prior art -- most of which was considered during prosecution -- in strained two- and three-reference alleged obviousness combinations that fail to establish invalidity. IONpath's attempt to throw all of these references against the wall does not stick -- particularly in light of the compelling evidence that the claimed inventions revolutionized the field. The pioneering advance is best exemplified by the words of IONpath's own founder Dr. Garry Nolan, who characterized the invention as revolutionary. Ex. G (FLUIDIGM_00059179) at -181 ("Nolan, who says he's not prone to hyperbole, calls the technology revolutionary. 'Scott's wonderful invention,' he says, 'is going to change the world of immunology, at the least.'"). As set forth below, summary judgment is required for both infringement and validity.

## I. THE INVENTIONS.

The '386 and '698 Patents claim a pioneering new method and system to perform multiplex analysis of biological samples at the single cell level. Ex. H (Kelly Rep.), ¶ 16; Ex. A, Abstract, 2:55-65. A plurality of analytes (such as different proteins or other biomarkers) in or on a plurality of cells are tagged with antibodies that are specific to the different analytes being analyzed. Ex. H ¶ 16; Ex. A, 4:35-46. Because each analyte has a different chemical structure, a specific antibody that will uniquely bind to that analyte is selected. Ex. H ¶ 16. Individual specific antibodies are tagged with a metal isotope -- an elemental tag that comprises a lanthanide or noble metal -- such that each elemental tag is identifiable by its mass. . Ex. H, ¶ 18; Ex. A, 9:56-10:19. Each elemental tag, when ionized, provides a distinct signal, so it is detectable and distinguishable by mass spectrometry analysis allowing for the identification of the corresponding protein or

biomarker to which the elemental tag-bearing antibody is bound. Ex. H, ¶ 18; Ex. A, 9:47-52. Because the elemental tag must be atomized and ionized into a gas phase to be detected and analyzed by mass spectrometry, the claimed method and system require, respectively, a step or device to "*vaporize, atomize, and ionize*" the multiple elemental tags. *See* Ex. H, ¶ 19; Ex. A, 30:55-31:12; Ex. B, 30:53-31:9.

Importantly, the claimed multiplexed method and system sequentially detect transient signals from multiple vaporized, atomized, and ionized elemental tags from each of the single cells, such that information about multiple analytes present on different individual cells can be determined. Ex. H, ¶ 19; Ex. A, 18:6-23. The ability to evaluate multiplex information at the cellular level was a pioneering breakthrough providing the ability to identify and understand multiple different proteins or biomarkers, and profile different cells to determine correlations between the presence and/or relative levels of such information and disease states. Ex. H, ¶ 17. Examples of areas where the claimed inventions have been implemented include cancer research and immuno-oncology, immunology, immunophenotyping, infectious disease/microbiology studies (for example, COVID-19), liquid biopsy, neurology, oncology, and stem cell research. *Id.*

## II. THE SHOWDOWN CLAIMS.

Pursuant to the Court's Order, Fluidigm selected Claim 9 of the '386 Patent, and IONpath selected Claim 6 of the '698 Patent, as their respective showdown claims. The claims are very similar with Claim 9 a method claim and Claim 6 a system claim.

## III. IONPATH'S MIBI PRODUCT INFRINGES BOTH SHOWDOWN CLAIMS.

IONpath's documents and witnesses establish that there are no genuine issues of material fact -- MIBI literally infringes both claims. MIBI indisputably: (1) tags multiple cells with antibodies chosen specific to different analytes, and the antibodies are tagged with elemental tags comprising a lanthanide or noble metal; (2) employs an ion gun to "*vaporize, atomize, and ionize*" the elemental tags on multiple cells; and (3) uses a time of flight mass spectrometer (TOF-MS) to sequentially detect and analyze transient signals of ionized elemental tags of different cells.

IONpath seeks to evade infringement by manufacturing arguments contradicted by its own documents, namely, that: (a) the *single element* of "*vaporizing, atomizing, and ionizing*" requires

adding an ordered *three-step* sequential process not mentioned in the patents; (b) "*vaporizing, atomizing, and ionizing*" requires "heat" (which is entirely absent from the patents); (c) the claims purportedly require the detection of the *entire elemental composition of each entire cell* – although the claims and patents are unequivocally only directed to detecting transient signals of the elemental tags (including every disclosed embodiment); and (d) IONpath's product allegedly does not sequentially analyze single cells using mass spectrometry. IONpath is wrong on all counts.

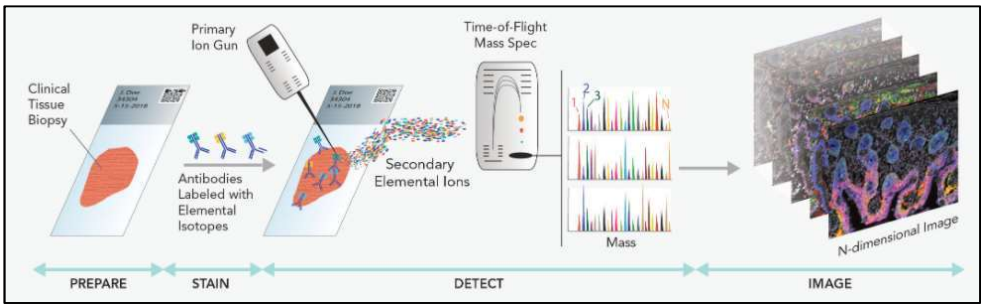
**A. IONpath's Infringing MIBI Technology.**

MIBI (Multiplexed Ion Beam Imaging) uses secondary ion mass spectrometry (SIMS) technology. MIBI is covered by and described in U.S. Patent No. 9,312,111, titled "Apparatus and Method for Sub-Micrometer Elemental Image Analysis by Mass Spectrometry" (the "MIBI Patent"). Ex. D. Three of IONpath's founders, Drs. Garry Nolan, Sean Bendall, and Robert Angelo, are named inventors on the MIBI Patent.[3] *See id.* at (72). [redacted]. IONpath also recently publis an article, which detail MIBI's elements and operation. *See* Ex. K (IONPATH_0039014) (the "LI Paper"). IONpath's website contains consistent information regarding the elements and operation of its infringing MIBI. *E.g.*, Ex. L ("How It Works").[4]

- **PREPARE**: FFPE tissue preparation follows conventional IHC protocols.
- **STAIN**: Tissue is stained with a mixture of validated antibodies with conjugated elemental reporters, in one single step.
- **DETECT**: Stationary tissue samples are raster-scanned with an ion beam and secondary elemental ions are generated.
- **IMAGE**: All markers are imaged at the same time and detected via TOF mass spectrometry

3/ Drs. Bendall and Angelo are also on IONpath's Board of Directors.

4/ [redacted]




An IONpath poster presentation likewise identifies MIBI's infringing attributes. *See* Ex. M ("MIBI Poster"). For example, the MIBI Poster explains: (1) "Samples were stained with a panel of 15 antibodies, each labeled with a specific metal isotope" (*i.e.* multiple cells tagged with a plurality of antibodies, and each antibody tagged with an elemental tag having a specific metal isotope); and (2) "Tissue is scanned via secondary ion mass spectrometry" (*i.e.* SIMS is used to "vaporize, atomize, and ionize" elemental tags, and analyze the transient signals from the vaporized, atomized, and ionized elemental tags). *Id.* ("Multiplexed Ion Beam Imaging (MIBI) [-] FFPE samples are processed similarly to traditional IHC except staining is performed with a panel of isotopically-labeled antibodies. … An ion beam rasters across the tissue liberating ions including the isotopes bound to the tissue via the antibodies. Time-of-flight mass spectrometry separates the labels based on mass for detection of markers present across the tissue.").

IONpath's documents establish that MIBI uses Fluidigm's claimed inventions employing: (1) antibodies labelled with elemental tags -- lanthanide and/or noble metal tags, which are tagged to analytes on multiple cells of interest (IONpath's branded reagents are called "MIBItags"); (2) a primary ion beam/gun that "*vaporizes, atomizes, and ionizes"* the elemental tags; and (3) a TOF-MS that is used to "analyze" the liberated elemental tags or ions from each cell. *See, e.g.,* Ex. K, at -15 to -17; Ex. D, 10:37-46.

While IONpath tries its best to avoid the fact, there is no question that MIBI detects and analyzes at a single cell level. Indeed, IONpath represents that MIBI performs the "simultaneous detection of 40+ markers at subcellular resolution, enabling single cell segmentation, cell type classification defined by markers with a wide range of expression levels, and spatial analysis of the cells present in the [tumor microenvironment]." Ex. K, at -15. IONpath's marketing materials

proudly tout MIBI's ability to perform single cell analysis. *See, e.g.,* Ex. N (description of Webinar by IONpath founder Sean Bendall) ("[A] novel combination of single cell analysis and metal isotopes based mass spectrometry (MIBI) … ."); Ex. O ("With MIBIscope™ ... [e]xpression can be measured at the single cell level with subcellular resolution while preserving spatial information").

IONpath's infringement is also confirmed by the many admissions of its own expert:

| **Claims 1 & 9 of the '386 Patent** | **Admissions of Dr. Winograd** |
|---|---|
| 1. A method of sequentially analyzing single cells by mass spectrometry: | Notwithstanding that the preamble is not limiting, Dr. Winograd's admissions confirm that MIBI sequentially analyzes single cells by mass spectrometry. [redacted] |
| providing a sample containing a plurality of antibodies of tagged cells tagged with a plurality of tagged antibodies, wherein each of the tagged antibodies is specific for a different analyte, and wherein each of the tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal; | [redacted] |
| vaporizing, atomizing, and ionizing multiple elemental tags from a single first cell of the plurality of tagged cells; | [redacted] |
| detecting, using mass spectrometry, the elemental composition of the first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell; | [redacted] |

| | |
|---|---|
| | [redacted] |
| vaporizing, atomizing, and ionizing multiple elemental tags from a single second cell of the plurality of tagged cells; | *See* "vaporizing, atomizing, and ionizing" admissions above. |
| detecting, using mass spectrometry, the elemental composition of the second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the second cell, wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially. | [redacted] |
| 9. The method of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope. | [redacted] |

There are no genuine issues of fact -- both IONpath's documents and the admissions of its own expert overwhelmingly establish that IONpath's MIBI infringes the Showdown Claims.

1. **Sample Having a Plurality of Tagged Cells.**

MIBI unequivocally meets all of the limitations of the first clause of Claim 1 of both the '386 and '698 Patents – tagging multiple cells of a sample with antibodies specific for different analytes, which antibodies are themselves tagged with lanthanide or noble metal elemental tags:

| **'386 Patent** | **'698 Patent** |
|---|---|
| Providing a sample containing a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the tagged antibodies is specific for a different analyte, and wherein each of the tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal; | Wherein the sample comprises a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the plurality of tagged antibodies is specific for a different analyte, and wherein each of the plurality of tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal; |

[redacted]

IONpath's documents likewise establish the identical facts. IONpath's MIBI Patent explains that the technology employs samples containing a plurality of cells (*e.g.* "a sheet of cells") that are "mass tagged" with identifiable elemental tags that include noble metals and

lanthanide. Ex. D, 3:32-35, 52-54. Consistently, IONpath's LI Paper and flowchart explain that MIBI: (1) prepares a tissue biopsy containing a plurality of cells by tagging/labeling cells with "antibodies labeled with elemental isotopes" ("metal labeled antibodies"). Ex. K, Fig. 1B, -16 ("Antibodies … were then conjugated to elemental tags using MIBItag conjugation kit … ."). IONpath's MIBI Poster explains that MIBI uses multi-cell biological samples by staining them with "isotopically-labeled antibodies" -- "a panel of 15 antibodies, each labeled with a specific metal isotope." *See* Ex. M. [redacted][6] IONpath advertises and sells the elemental tags (metal isotopes) identified in the LI Paper as part of its MIBItag Conjugation Kits. *See, e.g.*, Ex. K, at -16. There is no dispute of fact. IONpath's MIBI meets the first limitation of the showdown claims.

2. **"*Vaporizing, Atomizing, and Ionizing*" Multiple Elemental Tags.**

| **'386 Patent** | **'698 Patent** |
|---|---|
| Vaporizing, atomizing, and ionizing multiple elemental tags from a single first cell/single second cell of the plurality of tagged cells | A first device to vaporize, atomize, and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a single second cell of the plurality of tagged cells |

IONpath's documents and expert establish that the "*vaporizing, atomizing, and ionizing*"

[5] [redacted]

[6] The parties agree that elements having atomic numbers 57-71 are lanthanides. ECF 86-1, Ex. 1 to JCC, at 26.

limitations of the asserted claims read on the MIBI. The claimed inventions require a step or device to "*vaporize, atomize, and atomize"* the multiple elemental tags (*i.e.* lanthanide or noble metal tags) from a first and second cell of a sample to generate detectable ions. Ex. A, 30:63-65, 31:3-4; Ex. B, 30:62-64; Ex. H ¶¶ 61-63; *see also* Ex. A, Abstract, 6:51-55, 12:24-27, 13:2-4, 29:62-63. As the '386 Patent explains, the device used to liberate ions from the elemental tags may be "[a]ny means suitable" "to vaporize, atomize, and excite or ionize … the elemental tag …" Ex. A, 13:2-6. A POSITA at the time understood that the device applies energy to the elemental tags on the cells of interest, which generates ionized atomic components – i.e., detectable ions.[7] (Ex. H ¶¶ 65-66). Just as claimed, MIBI imparts energy from a "primary ion gun" on elemental tags on multiple successive cells to "*vaporize, atomize, and ionize"* the elemental tags and produce secondary elemental ions. *See, e.g.,* Ex. D, 10:37-46; Ex. M; Ex. L; [redacted]

MIBI's use of a "primary ion gun" to "*vaporize, atomize, and ionize*" elemental tags on a cell-by-cell basis performs the claimed *vaporizing, atomizing, and ionizing"* steps of Claim 1 of the '386 Patent, and is the "first device" of Claim 1 of the '698 Patent. *See, e.g.*, Ex. D, 10:37-43, Ex. M.[8]

Casting reality and its own admissions to the wind, IONpath props-up several strawmen to argue that MIBI's primary ion gun somehow fails to "*vaporize, atomize, and ionize*" the elemental tags**.** IONpath's argument is expressly contradicted by its own documents, the very patent it licenses and marks on its products, and its expert witness. [redacted]

[7] [redacted].

[8] IONpath seeks to add further improper limitations to the "first device" by trying to restrict it to four representative pieces of equipment described in the specification, namely a glow discharge, graphite furnace, CCP and/or IPC device (as well as a flow cytometry and/or particle injection system). The patents explain and POSITA understand that the "first device" incudes any suitable ion sources and ion generation techniques, including glow discharge and SIMS, and does not require a sample introduction device. Ex. H ¶¶ 91, 98.

[redacted] Indeed, even Dr. Winograd used "vaporization" to describe SIMS in articles he wrote for both *Science* and *Progress in Solid State Chemistry*. Ex. S at 810 ("[I]t is possible to use SIMS to detect molecular ions that are characteristic of the original sample. This approach has important implications in chemical analysis and offers a complementary mass spectrometric method for *vaporizing* and ionizing nonvolatile or thermally unstable compounds." (emphasis added)); Ex. T at 362 (very similar).

Not surprisingly, IONpath's founders' MIBI Patent is also consistent and explicitly states that the primary ion gun used in the accused MIBI (using SIMS based-technology) "*vaporizes, atomizes, and ionizes"* the sample segment (i.e., pixel) to produce secondary ions:

> "The material associated with the sample segment is *vaporized, atomized and ionized* by the primary ion irradiation unit 1010, and secondary ions associated with the sample segment are produced."

Ex. D, 10:40-43 (emphasis added). There is no ambiguity or dispute. IONpath's MIBI "*vaporizes, atomizes, and ionizes*" elemental tags at each pixel on the sample. IONpath's own licensed MIBI Patent says so. And, as IONpath's expert admits, as the MIBIscope raster scans across the tissue sample, that secondary ions are generated and detected from different pixels in different cells sequentially. Ex. C, 116:22-117:18.

IONpath disingenuously argues that its MIBI does not perform single cell analysis (*i.e.* "*vaporize, atomize, or ionize*" elemental tags from a first and second cell). But its own documents prepared outside of this litigation tell the true story and are littered with proclamations that MIBI

performs "single-cell analysis" and has "subcellular resolution." *See, e.g.,* Ex. N ("single cell analysis and metal isotopes based mass spectrometry (MIBI) offers a routine examination of 30+ parameters at the nanometer scale"); Ex. L ("How It Works") "Imaging at the sub-cellular resolution"). [redacted]

(a) **IONpath's "Heating" Argument.**

IONpath argues that MIBI allegedly cannot "*vaporize*" elemental tags because (a) vaporization allegedly requires "heat"; and (b) MIBI's primary ion gun purportedly does not employ "heat" as it "sputters" energy at the elemental tags. First, "heat" is not required by, and is entirely absent from, the asserted claims of the '386 and '698 Patents. Second, Dr. Winograd's testimony is fatal to IONpath's argument. [redacted]

IONpath's "heating" argument also fails on another level. "Sputtering," the technique MIBI's ion gun employs, is the *same* technique used by a "suitable device" for vaporizing, atomizing, and ionizing that is expressly identified in the asserted patents. The '386 and '698 Patents explicitly state that the device to perform, or perform the step of, "*vaporization, atomization, and ionization*" of elemental tags may be any "suitable device" and identifies four *non-limiting,* exemplary, types of devices: (1) glow discharge; (2) graphite furnace; (3) capacitively coupled plasma ("CCP"); and (4) inductively coupled plasma ("ICP"). Ex. A, 13:2-7; 7:31-41. To concoct its argument that the Court must import "heat" into the claims, IONpath seizes on only one exemplary device: ICP.[9] [redacted]

[9/] As Dr. Kelly explains, plasma temperature is merely the ICP-relevant descriptor for the kinetic energy of the ions to which the sample is exposed. Ex. H ¶ 77.

[redacted]

[redacted] Sputtering accelerates plasma ions at a sample, transferring kinetic energy upon impact, and results in surface material (ions) being ejected from the sample surface. *See* Ex. H (Ex. G to Kelly Report - Bogaerts) at 669 ("The use of the glow discharge as an ion source for mass spectrometry is based on the phenomenon of sputtering."); *see id.* (Ex. F to Kelly Report - Blades) at 16A ("The impinging ion . . . penetrates to a depth of a few angstroms where its kinetic energy can cause surface atoms to be ejected . . . a phenomenon called sputtering.") (alterations omitted).[10] IONpath's attempt to distinguish MIBI by asserting that it employs "sputtering," that "sputtering" does not employ "heat", and that "sputtering" is not taught by or covered by the asserted claims, is simply false. [redacted]

[redacted]

(b) **"*Vaporization, Atomization, and Ionization*" Does Not Require Separate Steps, Much Less Separating Gas Into Atomic Constituents.**

IONpath's second strawman is its contention that "*vaporize, atomize, and ionize"* must be performed in a "three-step sequence" – as well as another, unclaimed, fourth step of separating gas into atomic constituents. IONpath's "separate-steps" limitations are absent from, and not required by, the asserted claims. The specifications also expressly contradict IONpath's "three-step" argument as they explain that the term "*vaporization, atomization, and ionization"* does not require atomization, or vaporization following by ionization, and that all three can occur simultaneously or at different times. *See* Ex. A, 3:3-15; 13:7-9 ("vaporization, atomization, and ionization . . . can occur in different devices and at different times").[11] Further, "glow discharge,"

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10/ [redacted]; Ex. K, at -17 ("The MIBIscope rasters a primary ion beam across the tissue liberating secondary ions…"); *and* Ex. D, 8:7-12 ("... plasma … to produce a high brightness, focused ion beam for SIMS imaging analysis").

11/ "Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one." *Altiris, Inc. v. Symantec Corp.,* 318 F.3d 1363, 1369 (Fed. Cir. 2003) (quoting *Interactive Gift Exp., Inc. v. Compuserve Inc.,* 256 F.3d 1323, 1342-43 (Fed. Cir. 2001)). To determine whether "the steps of a method claim that do not otherwise recite an order, must nonetheless be performed in the order written" a two-part test is employed. *Altiris,* 318 F.3d at

identified in the '386 Patent, also undercuts IONpath's argument as it partially performs "*vaporization, atomization, and ionization"* simultaneously. Ex. H, ¶¶ 86-87.

IONpath's attempt to avoid infringement by asking the Court to import a "three-step" requirement into the claims runs directly afoul of the claims, specification, how IONpath's own founders, Board members, named inventors of the MIBI Patent, and POSITA use the term -- and would improperly eliminate one of the preferred devices disclosed in the patents-in-suit. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1277 (Fed. Cir. 2008) ("[W]here claims can reasonably [be] interpreted to include a specific embodiment, it is incorrect to construe the claims to exclude that embodiment, absent probative evidence on the contrary.").

3. **MIBI Detects Elemental Tags from First & Second Cells Using Mass Spectrometry.**

| '386 Patent | '698 Patent |
|---|---|
| Detecting, using mass spectrometry, the elemental composition of the first cell/second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell/second cell | A second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell/second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell/second cell |

The '386 Patent explains that the claimed invention uses a mass spectrometer (the "second device" of Claim 1 of the '698 Patent) to detect and analyze ions/isotopes generated from elemental tags bound to analytes in or on multiple cells. *See, e.g.,* '386 Patent, 7:56-61; 9:25-46 ("[T]his will allow for simultaneous detection of numerous biologically-tagged complexes"). Fluidigm's proposed construction of the identified limitations is: "*analyzing elements or isotopes of the elemental tags bound to analyte in or on the first cell [and second cell], by mass*

1369-70. A court looks first "to the claim language to determine if, as a matter of logic or grammar, they must be performed in the order written." *Id.* at 1369. If the claim language does not require an order, courts then "look to the rest of the specification to determine whether *it* 'directly or implicitly requires such a narrow construction.'" *Id.* at 1370 (emphasis in original) (quoting *Interactive Gift,* 256 F.3d at 1343). Neither part of the *Altrius* test is met here. The claim language does not require they be "performed in the order written" and the specifications cannot "directly or implicitly require[] such a narrow construction" as they state that "[i]n some instances, vaporization, atomization" may occur at the same time (Ex. A, 13:7-9), and explicitly state that, in some embodiments, "atomization may not be necessary, so that the term may or may not encompass vaporization followed by ionization directly." *Id.*, 3:5-7.

*spectrometry."* There can be no dispute that MIBI fully meets the above elements and limitations.

As described in IONpath's documents, there is no question of fact that IONpath's MIBI uses a TOF-MS (the "second device" of Claim 1 of the '698 Patent) to detect ions/isotopes liberated from metal conjugated antibodies affixed to analytes in or on multiple cells of a sample. *See*, *e.g.*, Ex. K, at -17 ("The mass of the secondary ions are determined using the orthogonal ToF mass spectrometer . . . ."); Fig. 1 ("Time-of-flight mass spectrometry separates the labels based on mass for detection of markers present across the tissue."); Ex. L (secondary ions are "detected via TOF mass spectrometry"); [redacted] IONPath's licensed MIBI Patent also memorializes this fact: "the detection of ion signals and data processing in Time-of-Flight (TOF) Mass Spectrometry …is described below." Ex. D, 10:62-67.[12]

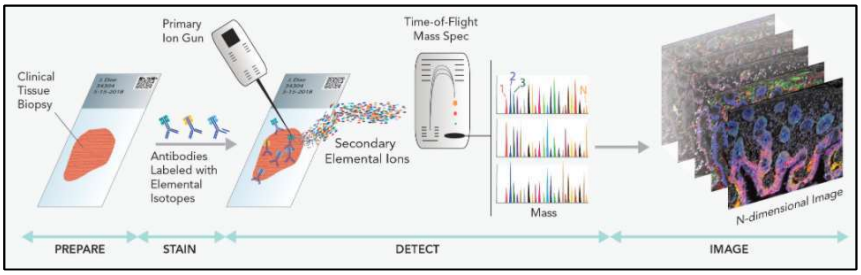
The asserted claims include the term "transient signal" of the first cell/second cell. The common meaning of the term "transient" is "lasting only for a short time" or "passing especially quickly into and out of existence." Similarly, the meaning of the word "signal" is detectable ions generated from the vaporized, atomized, and ionized elemental tags. *See, e.g.*, Ex. A, 5:52-59, 9:47-52, 17:21-38. As such, Fluidigm's construction of "transient signal," is: "*The detectable ions generated for a limited duration of time.*" Ex. H, ¶ 128. Fluidigm's construction is properly based upon the claims, specifications, and prosecution histories of the patents-in-suit, as well as what a POSITA would have understood at the time. IONpath fails to provide a construction for "transient signal." The Patents and claims are directed to mass spectrometry-based multi-parametric particle analysis which detects "transient signals" of ionized components that have a duration of microseconds -- "last for a period in the range of 20 to 200 microseconds." Ex. A, 18:8–10; Ex. H ¶ 128. The prosecution histories also confirm the fact that the transient signals are of limited duration in time. Ex. H, ¶ 129. [redacted]

[12/] IONPath also seeks to introduce limitations into the "second device" by requiring a specific mass spectrometry structure. These added limitations are unnecessary, as a POSITA would understand the implementation of mass spectrometry instrumentation to serve as the "second device" as claimed. Ex. H, ¶ 93.

[redacted]

(a) **Detecting Signals from Ionized Elements from First & Second Cells.**

IONpath erroneously argues that MIBI does not detect signals from secondary ions from first and second cells. To understand the fallacy of this argument, a further dive into the technology is helpful. MIBI admittedly performs the following steps:




1. MIBI sequentially "rasters a primary ion beam across" multiple cells having target biomolecules which have been tagged with antibodies tagged with elemental tags ("metal-conjugated antibodies"). (Ex. K, at -17). This results in secondary ions being liberated from the metal-conjugated antibodies associated with the target cells and biomolecules (*Id.*);

2. MIBI's TOF-MS then detects, analyzes, and ascertains the mass of the secondary ions, and assigns the detected ions to the corresponding "target biomolecules" on each cell (*Id.*);

3. MIBI creates a MIBItiff data file for all of the cells analyzed and imaged in the field of view of the device. (*Id.*)

IONpath's argument is, as we understand it, that because the width of the beam from the primary ion gun is smaller than the width of a cell, MIBI somehow cannot be detecting ionized elemental tags from successive cells (first and second cells). [redacted]

Not surprisingly, IONpath's own documents provide that MIBI's detection and analysis indisputably provides "single-cell," cell-by-cell, data – enough to determine cell boundary

locations, cell distances, spatial distributions, and "sub-cellular resolution" enabling segmentation and single-cell analysis. Ex. M; *see also* Ex. K, at -17; [redacted]

(b) **MIBI Detects the Elemental Composition of the Ionized Elemental Tags.**

IONpath attempts to side-step the statements in its own literature and advertising by asking the Court to apply a tortured construction requiring that all of the elements that make up each cell must be "discerned" and "detected." ECF No. 86-1, Ex. 1 to JCC, at 12-13. Not even the Patents' preferred embodiments perform IONpath's flawed construction. *See* Ex. H ¶ 111. Nor would it be possible. *See id.* ¶ 109. Aside from inviting error, IONpath's argument runs directly afoul of the claim language itself and would require the Court to read in an entirely new and inconsistent limitation. Both Claim 1 of the '386 and '698 Patents expressly require *only* that the mass spectrometer detect transient signals of the ionized elemental tags of each cell – which MIBI does using a TOF-MS ("second device"). The asserted claims do *not* require the detection of all of the elements comprising each cell. Ex. H ¶¶ 109-111.

The claims are directed only to detecting transient signals associated with ionized elemental tags to determine information regarding target analytes – not all of the elements that "make up the first cell." Indeed, the '386 Patent states that only the elemental composition of the tag is important.[13] Ex. A, 6:17-18 ("[I]t is only its elemental composition that is important."); 30:55–31:2 ("detecting a transient signal of the multiple vaporized, atomized, and ionized

[13/] IONpath erroneously asks the Court to read in yet more limitations into the claims, this time arguing that: (1) "detecting ... the elemental composition" ('386) or "detecting ... lanthanides or noble metals" ('698); as well as (2) the "first device" in '698, require a flow cytometry or other particle introduction device. Not only do the claims not contain any flow cytometry sample introduction structure or requirement, as they are not restricted to flow cytometry or a specific technique for sample introduction, the specification teaches embodiments that IONpath's construction would improperly exclude. For example, the Patents incorporate Baranov441 by reference which discloses laser ablation as a sample introduction technique. Ex. W ¶¶ 57-59. Moreover, the glow discharge technique identified in the Patents do not require a flow cytometry sample introduction technique. *See id.* ¶¶ 23-26 Also, IONpath's reliance upon the prosecution history associated with the Baranov441 reference is entirely off-the-mark. Baranov441 was distinguished during prosecution as it is not directed to and does not disclose the ability to perform single cell analysis, rather, it only performs bulk sample analysis. Ex. V ¶ 49. Sample introduction has absolutely nothing to do with this distinction.

elemental tags of the first cell"); Ex. H ¶¶ 110-111. Of note, IONpath's MIBI uses a TOF-MS to perform exactly what is claimed by the asserted patents -- detecting transient signals of the elemental tags of successive cells (at least first and second cells). Ex. K, at -17 (MIBI results in the release of secondary ions detected by a TOF-MS).

4. **IONpath's MIBI *Sequentially* Detects and Analyzes Transient Signals from First & Second Cells.**

| '386 Patent | '698 Patent |
|---|---|
| Wherein the transient signal associated with the first cell and the transient signal of the second cell are detected sequentially. | Wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially. |

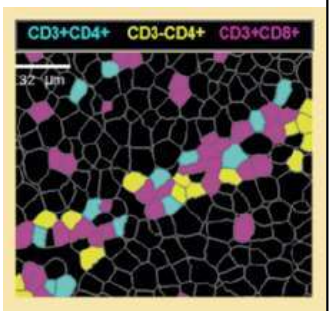
Fluidigm's proposed construction of the last two words of both Claim 1 of the '368 and '698 Patents, "detected sequentially," is "*observed at separate times.*" ECF 86-1, Ex. 1 to JCC, at 16. In other words, a transient signal associated with the first cell is detected before the detection of a transient signal associated with the second cell. [redacted]. There is no genuine disputed issue of fact that IONpath's MIBI uses a TOF-MS to detect and analyze transient signals associated with a first cell and a second cell, sequentially (i.e., at separate times).

[redacted]

MIBI's primary ion beam travels linearly across a sample striking one cell after another, sequentially. As the ion beam strikes the elemental tags on each cell, secondary ions are sputtered

from the precise locations of each elemental tag on each cell across the sample. [redacted] Because MIBI detects and analyzes transient signals of elemental tags from successive cells, and assigns each pixel or group of adjacent pixels to a unique cell integer, it performs "single-cell analysis" and "[p]reserves spatial information allowing … cell boundary and distance determination." Ex. M; *see also* [redacted] Ex. K, at -17, Fig. 1.

It should not be lost on the Court that IONpath employs the single cell data, detected and analyzed by the TOF-MS one cell after another, to map and generate images of the detected and analyzed sequential cell data. [redacted]




[redacted] IONpath's arguments cannot avoid its infringement.

5. **IONpath's "Analyzing" & "Post-Processing" Arguments.**

IONpath's contention that MIBI does not sequentially detect ionized elemental tags from successive cells until some later "post-processing" step is spurious -- as is IONpath's argument

that MIBI does not "analyze cells by mass spectrometry."[14] MIBI admittedly analyzes single cells using TOF-MS by detecting and analyzing transient signals of the vaporized, atomized, and ionized elemental tags. [redacted] Ex. D, 3:12-15 ("sequentially *analyzed* segments of a planar sample"), 8:45-49 ("[a] primary ion beam capable of producing elemental secondary ions may also be pulsed (sputtered), in order to release packets of mass ions into the TOF mass *analyzer* directly"), Abstract ("the *analyzer* being configured to separate secondary elemental atomic ions according to their mass-to-charge ratio by time of flight"), 10:43-45 & Fig. 4 (The ions are separated according to their charge-to-mass ratio by the Ion mass-to-charge ratio *analyzer* ..."), 1:40-41 ("The *analyzed* matrix includes, for example, biological tissue slices or cells that contain elemental information . . ."), 1:51-55 ("multiple TOF-MS scans on a continuous introduction of elemental ions from continuously *analyzed* two dimensional sample segments"), 2:17-20 ("the signal that indicates the presence of an elemental reporter in an *analyzed* sample segment in the mass spectrometer's main ion detector"), 2:56-57 ("a mass *analyzer* to separate the ions according their mass-to-charge ratio"); Ex. K, at -17 ("MIBIscope is a dynamic secondary ion mass spectrometer (SIMS) instrument with a time of flight (ToF) mass analyzer") ("single cell

[14] The preambles are not limiting. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,* 246 F.3d 1368, 1373-74 (Fed. Cir. 2001) ("If the body of the claim sets out the complete invention, and the preamble is not necessary to give 'life, meaning and vitality' to the claim, 'then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.'"). Nevertheless, "sequentially analyzing single cells" in the preamble would have the same meaning – a method or system to analyze transient signals associated with a first and second cell by mass spectrometry "*at separate times*."

analysis") ("[a]n electrostatic analyzer within the MIBIscope acts as an energy filter"), -18 ("each conjugated antibody was analyzed on the MIBIscope). IONpath's argument that MIBI's only "analysis" occurs somewhere downstream of MIBI is simply false.[15]

6. **IONpath's Antibodies are Tagged with a Distinct Isotopes.**

Showdown Claim 9 of the '386 Patent and Claim 6 of the '698 Patent each simply require that the tagged antibodies be tagged with a distinct isotope:

| Claim 9 -- '386 Patent | Claim 6 -- '698 Patent |
|---|---|
| The method of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope. | The method of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope. |

There is no dispute, or question of fact, that the antibodies IONpath uses with its MIBI are tagged with distinct isotopes and meet this limitation. [redacted] Ex. M ("Samples were stained with a panel of 15 antibodies, each labeled with a specific metal isotope"). [redacted] For at least these reasons, summary judgment of infringement on the showdown claims is required.

[15] At the risk of beating the proverbial "dead-horse," while asserting here that MIBI does not peform single-cell analysis, IONpath expressly advertises MIBI as performing "comprehensive single cell analysis." Ex. N.

## IV. THE CLAIMS ARE VALID.

Fluidigm respectfully moves the Court for summary judgment on invalidity (IONpath's First & Third Counterclaims and Second Affirmative Defense). IONpath cannot meet its burden to overcome the strong presumption of validity by clear and convincing evidence. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993-994 (Fed. Cir. 2009).

### A. The Claims Are Not Obvious.

In 2004, no prior art even considered the analysis of multiple elemental tags from a single cell, much less multiple different analytes in a single cell. Ex. V (Hieftje Validity Rep.) ¶¶ 36-37. As Dr. Hieftje explains, in 2004, there was no motivation to go the path of the claimed inventions, as it would have taken "an extreme leap of faith" and "extraordinary ingenuity" to conceive of the possibility. *Id.* Only with hindsight and armed with the patents (which is impermissible), would one even consider the claimed inventions. *See id.* IONpath cannot meet its burden to demonstrate by clear and convincing evidence that a POSIA "would have been motivated to combine" the numerous prior art references it seeks to hodge-podge together, as a POSIA at the time would not have "had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994.

- **U.S. Patent Publication No. 2002/0086441, Baranov et al. ("Baranov441").**

Baranov441 does not disclose or suggest single cell analysis, rather it is directed to "bulk" analysis over an entire sample (which could comprise 1000s of cells). Ex. V ¶¶ 46-47. Nor does Baranov441 disclose or suggest sequential single cell analysis, or the detection of multiple elemental tags used to tag antibodies specific for different analytes in or on a single cell. *Id.*

- **Nomizu, et al., J. of Analytical Atomic Spectrometry (2002) ("Nomizu2002").**

Nomizu2002 is not directed to, does not disclose, and does not suggest, the analysis of individual cells, nor any cell material, using mass spectrometry. *See* Ex. V ¶ 51. Rather, this reference is concerned with the detection of sub-micron airborne particles using a quadrupole mass spectrometer to detect an "element," namely zinc (which is not a lanthanide or a noble metal). *See id.* It only describes the detection of one highly abundant a zinc isotope (at least 6 million atoms of zinc per particle), and does not suggest detecting exogenously provided tagged antibodies (i.e. tagging with elemental tags), or the multiplexed detection of elemental tags to distinguish analytes

in or on an individual cell. *See id.* ¶¶ 51, 56.

- **Colliver, et al., Analytical Chemistry (1997) ("Colliver1997").** Colliver1997 is directed to the detection of highly abundant endogenous molecules (*i.e.,* potassium, sodium, and calcium), and large quantities of dopant materials (*i.e.* cocaine and DMSO), using TOF-SIMS techniques. Ex. V ¶ 63. It does not disclose or suggest techniques to perform the multiplexed detection of elemental tags used to tag antibodies to distinguish different analyte in or on a cell. *See id.* ¶ 63.
- **Kindness, et al., Clinical Chemistry (2003) ("Kindness2003").** Kindness2003 merely describes the detection of endogenous copper and zinc in liver tissue, using a laser ablation technique – and is not directed to single cells. *See* Ex. V at ¶ 71-73. Kindness2003 discloses that its laser ablation technique is not capable of resolving information on the single cell level. *Id.* at ¶ 71. It also expressly disavows a single cell analysis technique, and does not disclose or suggest the multiplexed detection of non-endogenous materials such as elemental tags. *Id.* ¶¶ 71-73.
- **Hindie, et al., Biology of the Cell (1992) ("Hindie1992").** Hindie is also off-the-mark, disclosing the detection of radioisotopes that have been metabolized and broadly taken up by cells (as opposed to targeting a specific analyte in the cells), using a SIMS technique. *See* Ex. V, ¶ 77. Hindie1992 does not disclose or suggest techniques that would provide for the multiplexed detection of elemental tags used to tag antibodies to distinguish different analyte in or on an individual cell. *Id.* ¶¶ 77-79.
- **Torchilin, et al., Current Pharmaceutical Biotechnology (2000) ("Torchilin2000").** Torchilin2000 is directed to polymeric contrast agents for medical imaging and does not disclose or suggest techniques for sequential single cell analysis by mass spectrometry, much less tagging antibodies to distinguish different analytes. Ex. V, ¶¶ 84-85.
- **Lauffer, et al., U.S. Patent No. 6,652,835 (2003) ("Lauffer835").** Lauffer835 is directed to contrast agents for diagnostic *in vivo* imaging, such as magnetic resonance imaging ("MRI"). Ex. V at ¶ 89. Lauffer835 does not suggest techniques for sequential single cell analysis by mass spectrometry. *Id.* ¶ 91.
- **King, et al., Mass Spectrometry Reviews (1990) ("King1990").** King1990 is a review paper describing fundamentals of glow discharge mass spectrometry. It is silent as to labelling of

a sample for analysis. *See* Ex. W ¶ 27. It also fails to disclose or suggest techniques that would provide for the multiplexed detection of elemental tags used to tag antibodies to distinguish different analyte in or on an individual cell. *Id.* ¶¶ 28.

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The asserted claims would not have been obvious at the time. None of the references teach, disclose, suggest, or would motivate POSITA to in any way combine mass spectrometry techniques with the use of elemental tags in a manner that would provide sequential single cell analysis.. Ex. V, ¶ 36; Ex. W, ¶ 38. Moreover, POSITA would have understood that the cited references not only fail to disclose or suggest how to devise instrumentation capable of detecting multiple elemental tags from a transient signal of a single cell, they actually *teach away* from attempting such analysis by, among other things, describing the limitations of detecting even highly abundant materials (e.g. endogenous materials) in biological tissues. *See* Ex. V, ¶ 104. POSITA would not have even sought to solve the problem of single cell analysis as they understood that existing techniques for performing subcellular analysis were lacking. Ex. V, ¶ 299-300 (citing 2003 article by Dr. Winograd describing deficiencies of subcellular analysis with TOF-SIMS). The considerations necessary for multiplexed single cell analysis only become clear in light of the guidance provided by the Patents. *See id.* The proposed combinations of references would not teach or suggest to POSITA the claimed inventions.[16]

IONpath founder Dr. Nolan perhaps summed up the ground-breaking nature of Fluidigm's patented inventions best, stating, "[this] invention … is going to change the world of immunology, at the least.'" Ex. G, at -181; *see also* Ex. X (Nolan Dep.) at 224:23-25 ("I told [Dr. Tanner] that we both should potentially [win the Nobel Prize] and in fact people have told me that we have been considered."). [redacted]

[redacted]

[16] IONpath's assertion of invalidity over prior SIMS and laser ablation references (Colliver1997, Hindie1992, Kindness2003) directly contradicts their position with respect to the patentability of their own licensed U.S. Patent No. 10,041,949 (with Dr. Nolan as inventor) covering MIBI, in view of SIMS references. *See, e.g.*, Ex. V ¶ 133 (citing to Amendment filed on Jan. 9, 2018).

[redacted]

**B. The Claims Have Proper Written Description and Are Enabled.**

IONpath bears the burden of establishing a lack of written description or enablement by clear and convincing evidence, which it cannot do.[17] *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App'x 961, 967 (Fed. Cir. 2014); *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). While IONpath contends that the patents fail to provide a sufficient written description to encompass a device that performs sputtering, the patents expressly describe and encompass technology – glow discharge -- that employs the same sputtering technique. Ex. V, ¶¶ 327-329. Further, the patents also identify laser ablation techniques.[18] Ex. W, ¶¶ 57-59. POSITA would understand that the patents contain a written description that encompasses vaporizing, atomizing, and ionizing elemental tags employing sputtering technology including glow discharge and SIMS. Ex. V, ¶¶ 328-329; Ex. W, ¶ 57.

IONpath's argument that an ion gun and/or raster scanning are not enabled is belied by its expert's admission that POSITA would know how to make and employ SIMS-based systems using an ion gun for vaporizing, atomizing, and ionizing certain elements. *See* Ex. V, ¶ 363. While IONpath provides nothing more than conclusory allegations of the need for optimization, configuration, and parameter-setting for it to make its infringing MIBI, no evidence has been provided to support such allegations—much less sufficient evidence to constitute clear and convincing evidence. *Id.*; *Cephalon*, 707 F.3d at 1339 ("Unsubstantiated statements indicating that experimentation would be 'difficult' and 'complicated' are not sufficient [to show lack of enablement]."). [redacted]

[17] "Compliance with the written description requirement is a question of fact but is amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *PowerOasis, Inc. v. T–Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed.Cir.2008).

[18] The Patents incorporate by reference Baranov441 (*see, e.g.,* Ex. A at 2:46-50, 4:35-45 and 9:15-20), which describes laser ablation of bulk materials.

[redacted] Similarly, IONpath's attempt to argue that the patents do not sufficiently describe or enable the use of laser ablation as a viable technique is also flawed. The patents expressly incorporate the Baranov441 reference, which discloses laser ablation as part of a device to vaporize, atomize, and ionize bulk tissue. Ex. W ¶¶ 57-59. Regardless of what suitable device(s) is used for vaporization, atomization and ionization, the patents enable detection of the elemental composition of transient signals from single cells.

IONpath's kitchen sink, multiple prior art reference, invalidity arguments are insufficient and the Court should grant Fluidigm summary judgment on those defenses.

## CONCLUSION

The admissions of IONpath's expert witness and founders compel summary judgment in this case. MIBI performs "single cell analysis" by detecting multiple "vaporized, atomized, and ionized" elemental tags on individual cells by ToF-MS. The inventions of the '386 and '698 Patents were "revolutionary," and revolutionary advances are far from obvious. IONpath's attempt to change the facts for this litigation should not be permitted to overcome what it repeatedly told the marketplace before this case began.

Dated: November 25, 2020

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**CERTIFICATE OF SERVICE**

I hereby certify that on November 25, 2020, I electronically filed the above document with the Clerk of the Court using CM/ECF which will send electronic notification of such filing to all registered counsel.

Dated: November 25, 2020 By: */s/ George G. Brell*